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14. ABSTRACT Diagnosis of oculomotor system deficits requires accurate knowledge of the binocular coordination dynamics, which have been studied only sparsely in humans. To provide such essential baseline data, Aim 1 will conduct the first large-scale study of a) the normal parameters of binocular coordination dynamics during saccades, vergence and accommodation, and b) the normal range of binocular coordination and vergence instabilities during reading. These parameters will be determined by fitting an advanced model of oculomotor dynamics to eye-movement data recorded with a binocular infrared eye tracker. For Aim 2, a suite of advanced functional MRI techniques will allow us to determine, for the first time in human, the oculomotor pathways in the brainstem for the major types of eye movement control, and establish the normal means and ranges of activation levels for each nucleus as a baseline for mTBI patients. For Aim 3 we will employ the methods for measuring the oculomotor dynamics of Aim 1 and fMRI protocols of Aims 2 to characterize the deficits in brainstem eye-movement control centers in mTBI patients.					
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TABLE OF CONTENTS

	Page
Introduction.....	3
Body.....	4
Key Research Accomplishments.....	12
Reportable Outcomes.....	13
Conclusion.....	13
References.....	13
Appendices.....	14

INTRODUCTION:

To provide essential baseline data on the normal parameters of binocular coordination dynamics, Aim 1 will conduct the first large-scale study of a) the normal parameters of binocular coordination dynamics during saccades, vergence and accommodation, and b) the normal range of binocular coordination and vergence instabilities during reading. These parameters are determined by fitting a multifactorial model of oculomotor dynamics to eye-movement data recorded with a binocular infrared eye tracker.

BODY

SECTION 1: AIMS

Progress is specified under the items specified in the SOW:

Preliminary administrative functions.

1. Complete and submit human subjects documents to the IRB committee of record for this study. *1 month*

All human subjects documents for both the Smith-Kettlewell and the Palo Alto VA components of the project were submitted to the USAMRMC ORP HRPO within the specified 30-day period.

2. On receipt of award notice, complete human subjects documents to the Surgeon General's Office for review and approval. *3-6 months*

The documents for both institutions have all been reviewed by the USAMRMC ORP HRPO, revised, reapproved and resubmitted to the USAMRMC ORP HRPO.

Aim 1. Characterize norms and anomalies in binocular coordination dynamics for a large control population (two-year project beginning in Year 1)

1a. Run normative studies of binocular coordination dynamics for eight kinds of binocular eye movements in 100 normal adults age-matched to the VA TBI population. *12 months*

1b. Perform individual analyses of the performance indices for the eight types of binocular coordination dynamics as data become available from sub-aim 1a. *11 months (concurrent with 1a)*

1c. Perform preliminary dynamical modeling and statistical analysis of normative oculomotility distributions to define 12 subjects within $\pm 1s$ of the means on all oculomotility criteria. *1 month*

1d. Perform ongoing dynamical modeling of normative oculomotility data records. *9 months*

1e. Perform full statistical analysis of normative oculomotility distributions. *3 months*

1f. Complete data analysis, literature review in relation to results, and paper writing. *5 months*

The main aim for Year 1 is the normative studies of binocular coordination dynamics. Human subjects approval was granted on May 2nd, 2011, before which we implemented the detailed software for running and analyzing the 8 oculomotor tasks in relation to the binocular oculomotility recorder. For each task, this first requires both identifying each event and isolating i) rapid executive saccades, ii) microsaccades, iii) fast and iv) slow vergence movement components, v) blinks and vi) oculomotor drift from the records. Thus, for each type of eye movement, we developed the analysis to compare the oculomotility parameters for the two eyes in order to quantify its degree of binocular coordination. These capabilities were completed in the first quarter and debugged for practical use in the second quarter.

One of the goals of this research was to validate the use of the economical and convenient Visagraph III binocular eyetracker for this kind of research. We demonstrated that it has a noise level of about 2 arcmin, well below the requisite level for binocular vergence eye movements of the order of 30 arcmin or above, and is capable of measuring the saccadic main sequence for saccades of 5° or greater to an accuracy comparable with that of the best reported eyetrackers.

In the meantime, the P.I. was active on the organizing committee for a TBI symposium at his home institution, Smith-Kettlewell, entitled 'Visual Function and Its Management in mTBI' (March 4-5th), which is planned to be the first of a continuing series of biannual meetings to encourage interest in this field of medical research. The P.I. and Dr. Goodrich were two of the speakers at this meeting, which was highly praised for providing a full assessment of progress in vision research in relation to mTBI. We have also been scheduled for presentations based on the material provided in the original proposal to:

- the 8th Annual World Congress on Brain, Spinal Cord Mapping & Image Guided Therapy in San Francisco on June 8-10, 2011,

- the Federal Interagency Conference on Traumatic Brain Injury in Washington D.C. on June 13-15, 2011.
- the Association for Research in Vision and Ophthalmology, May 6-10, 2012.

SECTION II – PROGRESS TO DATE:

Experimental Studies

The main aim for Q4 is a continuation of the normative studies of binocular coordination dynamics. As per the QPR-3, the oculomotor dynamics tests are:

0) Calibration procedures

- A) Pretest horizontal position calibration series for both eyes.** The fixation target undergoes two randomized sets of horizontal position shifts over the range from -20° to 20° with button presses indicating when fixation is accurate at each position. (Saccades from this calibration series can be used to specify the main sequence of horizontal saccadic velocities for the both eyes operating together, and also provide the fixation angles to assess the phoria angle under each eye viewing for uniocular tests B and C.)
- B) Pretest horizontal position calibration series for the left eye.** The fixation target undergoes two randomized sets of horizontal position shifts over the range from -20° to 20° with button presses indicating when fixation is accurate at each position. (Saccades from this calibration series can be used to specify the main sequence of horizontal saccadic velocities for the left eye.)
- C) Pretest horizontal position calibration series for the right eye.** The fixation target undergoes two randomized sets of horizontal position shifts over the range from -20° to 20° with button presses indicating when fixation is accurate at each position. (Saccades from this calibration series can be used to specify the main sequence of horizontal saccadic velocities for the right eye.)

1) **Horizontal binocular fixed saccades.** Binocular eye movements are recorded while the fixation target undergoes horizontal square-wave position changes every 2-3 s at $\pm 10^\circ$, which is comfortably within the saccadic range for normal subjects. This test assesses both the variability and the fatigability of a sustained sequence of repeated saccades.

2) **Horizontal binocular variable-amplitude saccades.** Binocular eye movements are recorded while the fixation target undergoes horizontal square-wave position changes every 2-3 s over a range of amplitudes up to $\pm 10^\circ$. This test assesses both the main sequence parameters for horizontal saccades.

D) **Practice reading.** The subject reads an elementary-grade reading text from the standardized Readalyzer test set to become comfortable performing the reading task.

3) **Elementary-grade reading.** Binocular eye movements are recorded while subject reads an elementary-grade reading text from the standardized Readalyzer test set to measure the full scope of binocular coordination during basic reading.

4) **High-school-grade reading.** Binocular eye movements are recorded while subject reads an elementary-grade reading text from the standardized Readalyzer test set to measure the full scope of binocular coordination during advanced reading.

5) **Rapid horizontal disparity vergence jumps.** Binocular eye movements are recorded while the fixation target undergoes horizontal square-wave disparity change every 2-3 s (with random jitter from a uniform distribution) which are optimal conditions for completion of repeated normal vergence movements.

6) **Slow horizontal disparity vergence tracking.** Binocular eye movements are recorded while the fixation target undergoes a continuous horizontal sinusoidal disparity change of 0-2° at 0.25 Hz, which is comfortably within the vergence range for normal subjects.

7) **Slow horizontal binocular tracking.** Binocular eye movements are recorded while the fixation target undergoes a continuous horizontal sinusoidal motion of 0-2° at 0.25 Hz, as an in-phase control for the vergence tracking.

8) **Full-cue vergence jumps.** Binocular eye movements are recorded while near and far targets viewed binocularly (with a small vertical displacement between the targets to avoid mutual occlusion) are switched at 0.25 Hz, signaling the subject to make a vergence movement to make near/far verge between them.

E) **Interim horizontal position calibration series for both eyes.** The fixation target undergoes two randomized sets of horizontal position shifts over the range from -20 to 20° with button presses indicating when fixation is accurate at each position. (This posttest is required to assure stability of the calibration during the long series of horizontal eye movement measures).

9) **Accommodative vergence jumps (left fixation).** Binocular eye movements are recorded while near and far targets viewed with the left eye (with a small vertical displacement between the targets to avoid mutual occlusion) are switched alternately on and off at 0.25 Hz, signaling the subject to switch fixation between them

10) **Accommodative vergence jumps (right fixation).** Binocular eye movements are recorded while near and far targets viewed with the right eye (with a small vertical displacement between the targets to avoid mutual occlusion) are switched alternately on and off at 0.25 Hz, signaling the subject to switch fixation between them.

F) **Posttest horizontal position calibration series for both eyes.** The fixation target undergoes two randomized sets of horizontal position shifts over the range from -20 to 20° with button presses indicating when fixation is accurate at each position. (This posttest is required to assure stability of the calibration during the long series of horizontal eye movement measures.)

G) **Vertical position calibration series for the left eye.** The fixation target undergoes two randomized sets of vertical position shifts over the range from -16 to 16° with button presses indicating when fixation is accurate at each position. (Saccades from this calibration series can be used to specify the main sequence of vertical saccadic velocities for the left eye.)

H) **Vertical position calibration series for the right eye.** The fixation target undergoes two randomized sets of vertical position shifts over the range from -16 to 16° with button presses indicating when fixation is accurate at each position. (Saccades from this calibration series can be used to specify the main sequence of vertical saccadic velocities for the right eye.)

11) **Vertical binocular fixed saccades.** Binocular eye movements are recorded while the fixation target undergoes vertical square-wave position changes every 2-3 s at $\pm 10^\circ$, which is comfortably within the saccadic range for normal subjects.

12) **Vertical binocular variable-amplitude saccades.** Binocular eye movements are recorded while the fixation target undergoes **vertical** square-wave position changes every 2-3 s over a range of amplitudes up to $\pm 10^\circ$. This test assesses both the main sequence parameters for **vertical** saccades.

Recruitment

The total number of subjects recruited for the normative study is 78, of whom 64 passed the screening test and 54 have taken the full oculomotor test battery and clinical history to date. Of those tested, 41 individuals passed the inclusion criterion of having no clinical history of brain or ocular abnormalities, while 12 failed the criteria for normality. Of these, 8 individuals had residual oculomotor symptoms from a past TBI incident, 2 had a

history of head trauma with no symptoms, 2 had nystagmus and one had strabismus. We note that the 1-year target for completing the normative testing is May 2nd, 2012. We are on track to have the project completed by this target date.

After testing 50 subjects, the testing was put on hiatus for two months while we developed further analyses of the data from the first 50 subjects that we had run. These analyses revealed that the some subjects were experiencing unanticipated difficulty with the screen-based disparity tracking task, so we are now including the full-cue disparity tracking task based on the alternating lights at different distances developed for the accommodative vergence task, by viewing those lights binocularly. They therefore incorporate 4 distance cues for vergence – disparity, accommodation, size, and knowledge physical distance (the proximal vergence cue). This condition tests that any deficiency in the disparity vergence is not due to disparity processing per se but to a deficiency in the oculomotor plant controlling the vergence movement.

Recruitment of mTBI subjects from the VA Palo Alto had to be delayed because the entire unit was physically moved from the Palo Alto campus to the Menlo Park campus in December to accommodate construction of a new Center building; this move disrupted routine activities for over two months. They are now settled into the temporary building and recruiting has been restarted. As a result, in combination with a slow rate of acceptance of the opportunity to participate in the study among the candidates approached, 4 mTBI cases have been recruited through the Polytrauma Network Clinic, of whom 1 has been enrolled in the study.

Data Analysis

Oculomotor time series analysis

In the last quarter, we finalized the implementation of the detailed software for running and analyzing the time series of the 8 oculomotor tasks for this study in relation to the binocular oculomotility recorder. For each task, this first requires both identifying each event and isolating i) rapid executive saccades, ii) fast adaptive and iii) slow sinusoidal versional and iv) vergence movement components, v) microsaccades, vi) blinks and vii) oculomotor drift from the records.

It was the computational goal of the current reporting period to develop the computational framework for the comparison the oculomotility parameters for the kind of eye movement in the two eyes in order to quantify the accuracy of binocular coordination for each type. The full analysis consists of the estimation of 180 parameters of the individual and relative binocular coordination behavior during the 8 oculomotor tasks, together with the 8 calibration conditions. The first task was to develop general analyses for each type of eye movement. These analyses are illustrated in Figs. 1-6. See captions for details.

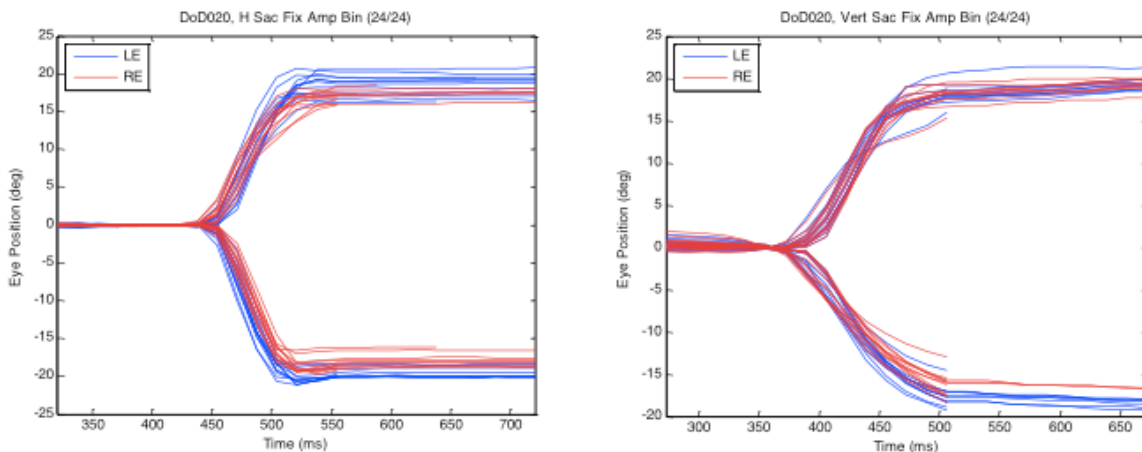


Fig. 1. Examples of fixed amplitude 20° saccades in the horizontal (left panel) and vertical (right panel) directions for the left eye (blue traces) and right eye (red traces). Note the slowing in the vertical saccade waveforms.

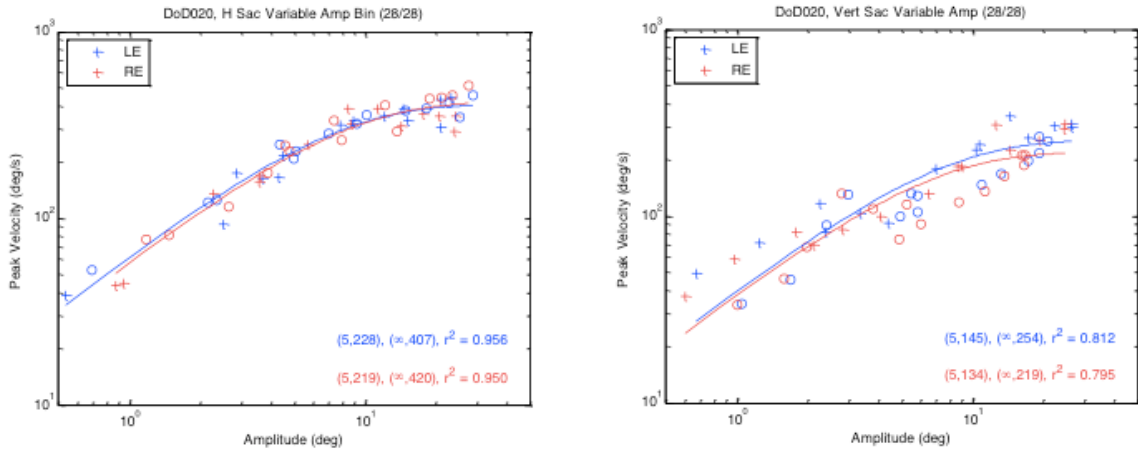


Fig. 2. Examples of saccadic main sequence plots of peak velocity vs amplitude in the horizontal (left panel) and vertical (right panel) directions for the left eye (blue traces) and right eye (red traces). Note the slowing across the amplitude range in the vertical saccades in the downward (circles) vs the upward (crosses) direction.

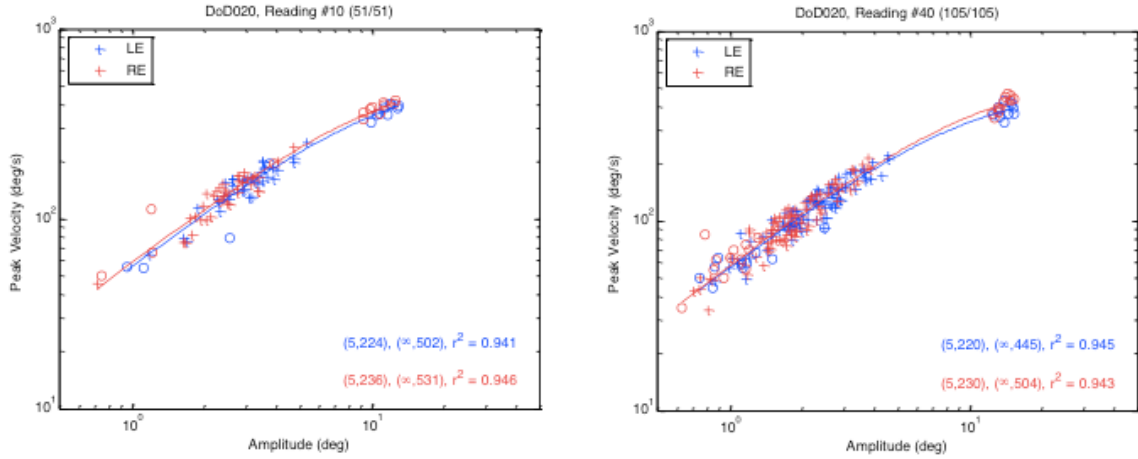


Fig. 3. Examples of horizontal saccadic main sequence plots of peak velocity vs amplitude for easy (left panel) and difficult (right panel) reading texts for the left eye (blue traces) and right eye (red traces). The data are fitted by the standard model for the saccadic main sequence. Note the increased proportion of small-amplitude saccades for the more difficult reading task and the similarity in the fitting parameters for the two difficulty levels.

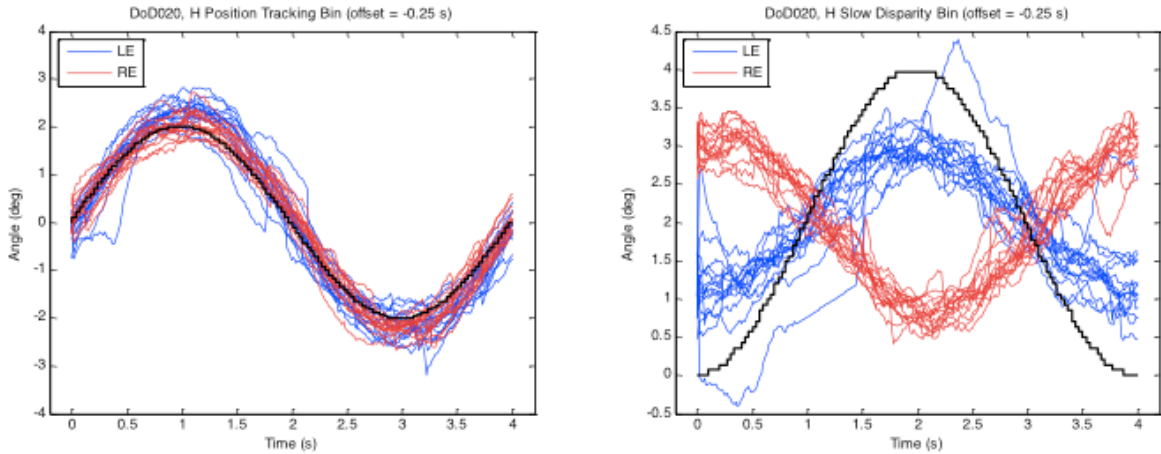


Fig. 4. Examples of sinusoidal position tracking (left panel) and disparity tracking (right panel) for the left eye (blue traces) and right eye (red traces). The black line indicates the trajectory of the position or disparity target, respectively..

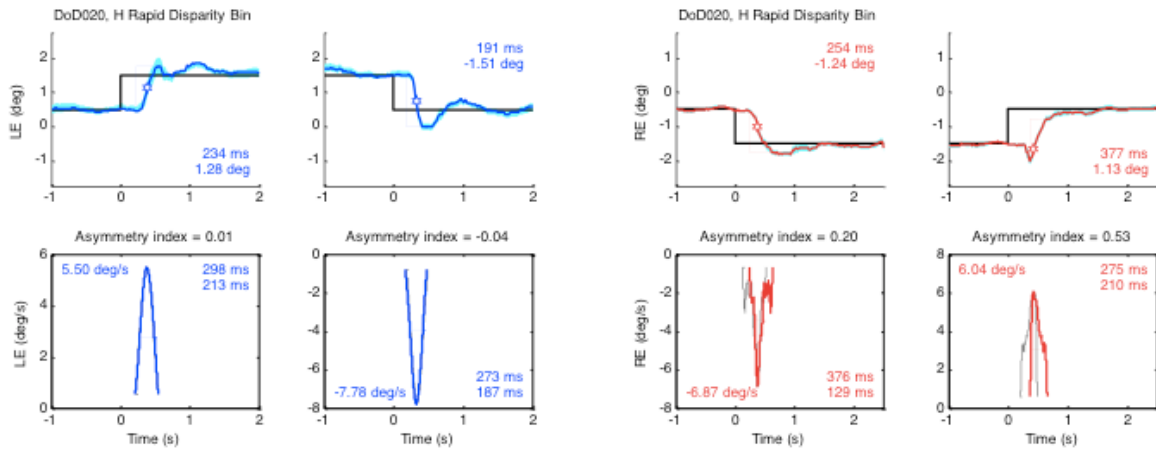


Fig. 5. Examples of the rapid disparity convergence and divergence analysis plots for the left eye (blue traces) and right eye (red traces). The left subpanels are the vergence position and velocity traces, while the right subpanels are the divergence position and velocity traces. The stimulus position change is indicated by the black line. The cyan shading zone in the upper plots represents \pm standard error of the mean along the position traces. The gray trace in the lower plots shows the time-inverted velocity profile aligned with the peak velocity, as an indicator of the waveform asymmetry.

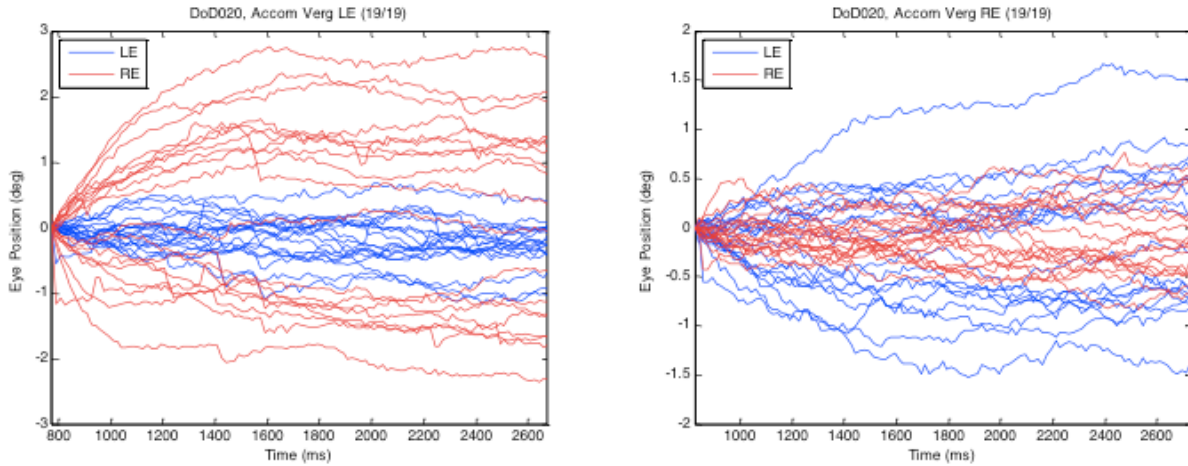


Fig. 6. Examples of the accommodation convergence and divergence binocular analysis plots for left-eye fixation (left panel) and right-eye fixation (right panel), each for the left eye (blue traces) and right eye (red traces) movements. Note that the (covered) right eye is expected to show vergence movements for left-eye fixation, and vice versa. The traces show that the oculomotor dynamics are generally consistent with the predictions, though generally noisier under these monocular viewing conditions and with a time course of about 1 s, dramatically slower than the disparity vergence dynamics of Fig. 5.

Example saccadic analysis

The primary variables of saccadic dynamics are the onset time, duration, amplitude, and peak velocity. In addition, there is the question of the saccadic waveform, which may be time-symmetrical relative to the point of peak velocity or may show asymmetric rise and fall times of the velocity trace. To provide the analysis of the saccadic dynamics, we used the model waveform of a raised-cosine function to the computed velocity trace of the saccade time courses. To determine the asymmetry, we identified the peak velocity on a smoothed version of the velocity trace and fitted a waveform model consisting of the sum of a raised-cosine and an exponential decay with appropriate time-constant to the velocity time course. The ratio of the raised-cosine to the exponential component determined the asymmetry index. The onset time and duration were determined by the 1% points of the fitted function.

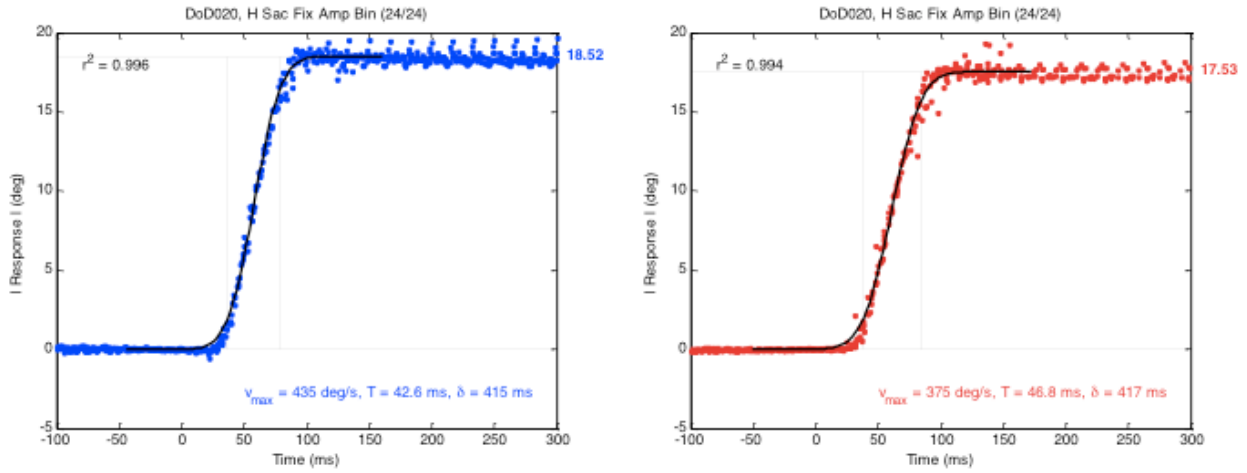


Fig. 7. Examples of the horizontal saccade fits to the are the overlay of the 12 fixed saccades, aligned in time and normalized in amplitude, for the left eye (left panel) and right eye (right panel), with the dashed lines indicating the values used for the distributions. Note the very values for variance accounted for. (The zero on the time axis is derived from the alignment process and does not relate to the saccadic latency values.

Examples of the function fitting to the raw saccade traces are shown in Fig. 7. The fixed saccade paradigm consists of measuring a sequence of 12 saccades to jumps of stimulus position from -10° to 10° on either side of fixation at times jittered by 1s around a fixed alternation rate (in order to measure response latency without contamination from predictive movements). The data are the overlay of the 12 fixed saccades, aligned in time and normalized in amplitude, illustrating the high repeatability of the saccadic waveforms. The black line is the model fit. Note that the proportion of variance accounted for is of the order of 0.995, indicating that the residual variance both across saccades and between the model fit and the saccadic waveform is substantially less than 1% of the overall variance. The five main parameters for the saccadic analysis are the onset time of the saccade, its duration, its amplitude, its peak velocity and the symmetry of the time course preceding and following the time of the peak velocity.

Example histogram analysis

To illustrate the capabilities developed to this point, the parameter analysis for the 41 normal subjects is shown in Fig. 8. There was no significant difference in the distributions for the left and right directions for horizontal saccades, so their parameters are combined across the two eyes. Upward and downward saccades are, however, plotted separately as they showed significant deviations in their dynamic parameters from the horizontal predictors.

The saccade distributions for the interim analysis of the normal group show a number of interesting features. First, overall the distributions are well fit but the Gaussian model, particularly for the horizontal eye movements (left panel in Fig. 8), with an effect size (the reciprocal of the coefficient of variation). For most parameters, the primary effect sizes were of the order of 10, dropping as low as about 5 for the peak velocity measure. This means that the population norms are giving good quality measures of their parameter values with sufficient reliability to measure individual deviations of the order of 10% of the average value (or 20% for the peak velocity).

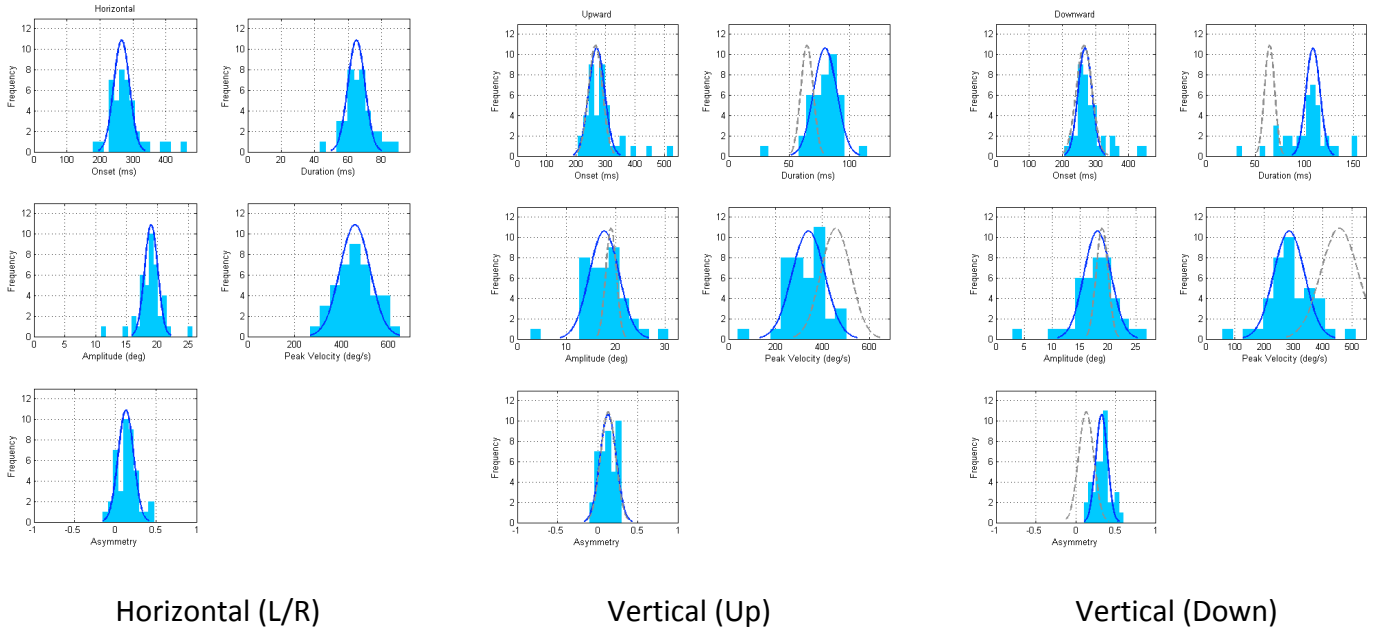


Fig. 8. Distributions of the parameters of oculomotor dynamics for horizontal (aerage left-right), vertical upward and vertical downward saccadic eye movements. Blue curves are best-fitting model Gaussian distributions after iteratively removing outliers (Winsorizing). Dashed gray curves are horizontal Gaussian fits replotted on the vertical distribution plots for comparison. The five panels in each case are for saccade onset time, saccade duration, saccade amplitude, saccade peak velocity and saccade waveform asymmetry, respectively. Note large deviations of some parameter distributions for vertical saccades from those predicted from the horizontal saccade distributions, and the upward downward differences.

The second property that can be seen in these distributions is that some individual cases can be categorized as outliers relative to the main (Winsorized) Gaussian model. For the horizontal distributions, $\sim 95\%$ of the cases fall within the predicted form of the distribution, but there are respectively 3, 2, 3, 0 and 1 outliers for the onset time, duration, amplitude, peak velocity and waveform asymmetry parameters, respectively. On each parameter, therefore, a very few individuals can be categorized as performing abnormally relative to the typical population dynamics. This factor will need to be built into the definition of abnormality for the assessment of the degree of abnormality in the population of TBI sufferers.

We can use the vertical saccades as a model system for comparing different forms of eye movements, based on the predicted parameters from the horizontal eye movements. While the distributions are strikingly similar for the onset latency parameter, for both upward and downward saccades, large differences are seen in the other parameters. For both directions, the vertical saccades are significantly longer in duration, significantly more variable in amplitude, and significantly lower in peak velocity than the horizontal saccades. The downward saccades are also significantly more asymmetric than either the horizontal or upward saccades. In several cases these differences would be diagnostic for about half the population for upward saccades and 2/3rds of the population for downward saccades (relative to the 1% points on the horizontal parameters distributions). While we stress that these are normal results for the vertical saccade distributions, they illustrate how the identification of abnormal saccadic dynamics would proceed in the case of a population of mTBI sufferers. Thus, it can be seen that the physiological variations in saccadic parameters fall well within a range to be readily measurable within the noise levels of our present techniques.

Another question that can be asked about these distributions is whether they represent the inherent measurement variability or the true variation of the parameters among the subject population. One measure that can be taken for this purpose is the ratio between the differences in distributions of the parameters *between* eyes to the distributions of the average *across* the two eyes. If this ratio is close to 1, it implies that the observed variability is mostly measurement error, while if it is much smaller than 1, it implies that is mostly population variance.

Finally, if this ratio is much larger than one, it implies that the two eyes tend to be more different than their population average, a form of anticorrelation between the eyes in which a dominant eye that is stronger than average has a reciprocal effect on the fellow eye to make it weaker than average.

Expressed in terms of root mean square (RMS) values, the difference/joint RMS ratio was about 1 for the amplitude, the duration and the peak velocity parameters (except for downward saccades) implying that the variance on these parameters was largely measurement noise. The exception was for the duration of downward saccades, which had a difference/joint RMS ratio of 2.6, implying some degree of dominant/suppression relationship between the control centers for this form of eye movement. An even stronger value averaging ~5 was seen for the difference/joint RMS ratio of the asymmetry parameter, implying a tendency for opposite asymmetries in the two eyes.

SECTION III – PROBLEM AREAS:

As specified under Recruitment, the recruitment of mTBI subjects from the VA Palo Alto had to be delayed because the entire unit was physically moved from the Palo Alto campus to the Menlo Park campus in December to accommodate construction of a new Center building; this move disrupted routine activities for over two months. They are now settled into the temporary building and recruiting has been restarted. However, a further problem will arise when they have to move back to their new building in the next few months. Combined with the unexpectedly slow rate of referral of mTBI cases to the Polytrauma Network Clinic recently, we anticipate a relatively low rate of recruitment from this source.

Seeing this situation developing, we noted the high rate of mTBI cases in our normative recruitment population, who are excluded from the normative sample on the basis of their mTBI history. We have nevertheless gone ahead with testing these individuals, and will be cumulating them into appropriate categories of severity and recency of the mTBI incidents in order to evaluate their oculomotor status relative to that of the normative sample.

SECTION IV – WORK TO BE PERFORMED:

The next quarter will involve completion data collection for the normal control participants. We expect to complete the battery analysis techniques for the oculomotor dynamics for all parameters of each each, to form the primary database of analytic parameters for the normative study. We will also begin testing for the functional imaging studies of the normative function of the brainstem oculomotor nuclei.

KEY RESEARCH ACCOMPLISHMENTS:

- Human subjects document submission completed
- Software for Aim 1 completed
- Successful involvement in organizing a local meeting on mTBI.
- Half the normative recruitment achieved
- 10 mTBI cases recruited
- Primary oculomotor dynamics analysis suite completed
- Nine meeting presentations

REPORTABLE OUTCOMES:

Abstracts:

- Good WV, Tyler CW. TBI overview and Orientation. **Visual Function and Its Management in mTBI**. Smith-Kettlewell Eye Research Institute, March 4-5, 2011.
- Goodrich GL. Neurologic vision impairment: A new direction for low vision research and rehabilitation. Paper presented at the **10th International Low Vision Conference**, Kuala Lumpur, Malaysia, Feb 20-24, 2011.
- Goodrich GL. Impacts on vision function – including early and late onset -- what we know and don't know. **Visual Function and Its Management in mTBI**. Smith-Kettlewell Eye Research Institute, March 4-5, 2011.
- Harris O, Goodrich GL, Cockerham G, Schuchard R. TBI and vision loss: A continuum of care. **3rd Federal Interagency Conference on Traumatic Brain Injury**, Washington DC, June 13-15, 2011.
- Tyler CW. Potential for brain imaging in mTBI. **Visual Function and Its Management in mTBI**. Smith-Kettlewell Eye Research Institute, March 4-5, 2011.
- Tyler CW, Likova LT, Goodrich GL. Brainstem/midbrain imaging for oculomotor dysfunction in mild traumatic brain injury. **8th Annual World Congress on Brain, Spinal Cord Mapping & Image Guided Therapy**. San Francisco, June 8-10, 2011,
- Tyler CW, Likova LT, Goodrich GL. Oculomotor dysfunction in mild traumatic brain injury. **3rd Federal Interagency Conference on Traumatic Brain Injury**, Washington DC, June 13-15, 2011.
- Tyler CW, Elsaid, AM, Likova LT, Goodrich GL. Analysis of human vergence dynamics. **Association for Research in Vision and Ophthalmology**, Fort Lauderdale, FL, May 5-10, 2012.

Awards:

Dr. Goodrich received the first 'Tiresias' award from the International Society for Low Vision Research and Rehabilitation (ISLRR) during the 10th International Low Vision Conference in Kuala Lumpur, Malaysia. The award recognized Dr. Goodrich's major role in the development of the field of rehabilitation and research on visual impairment. (Tiresias was given the gift of prophecy by the gods in recompense for being blinded by the jealous Queen of the Gods, Hera.)

CONCLUSION:

The project is well under way, with the data collection for Year 1 more than half completed and the data analysis for the oculomotor dynamics advancing in good form. We note that the delayed start on the human subjects approval did delay the the data collection effort, but we expect to have the full normative dataset completed by the one-year anniversary of the human subjects approval.

REFERENCES:

N/A

APPENDICES:

Brabyn JA, Jampolsky AJ, Good VW, Tyler CW (Organizing Committee). **Visual Function and Its Management in mTBI**. Symposium at The Smith-Kettlewell Eye Research Institute, San Francisco, March 4-5, 2011.

Goodrich GL. Neurologic vision impairment: A new direction for low vision research and rehabilitation. **10th International Low Vision Conference**. Kuala Lumpur, Malaysia, Feb 20-24, 2011.

Tyler CW, Likova LT, Goodrich GR (2011) Brainstem/midbrain imaging for oculomotor dysfunction in mild traumatic brain injury. **8th Annual World Congress on Brain, Spinal Cord Mapping & Image Guided Therapy**. San Francisco, June 8-10, 2011,

Tyler CW, Likova LT, Goodrich GR (2011) Oculomotor dysfunction in mild traumatic brain injury. **Federal Interagency Conference on Traumatic Brain Injury**, Washington D.C, June 13-15, 2011.

Tyler CW, Elsaid, AM, Likova LT, Goodrich GL. Analysis of human vergence dynamics. **Association for Research in Vision and Ophthalmology**, Fort Lauderdale, FL, May 5-10, 2012.

Visual Function and Its Management in mTBI

**A Symposium at
The Smith-Kettlewell Eye Research Institute
San Francisco
March 4-5, 2011**

Organizing Committee: John Brabyn, Ph.D. (chair)
Arthur Jampolsky MD
William Good MD
Christopher Tyler PhD

Preliminary Program

Friday March 4

8:45 am Registration and coffee

9:15 Welcome

Arthur Jampolsky MD

9:20 Introductory Remarks

Col Donald Gagliano MD, Executive Director, DoD/VA Vision Center of Excellence

Col Robert Mazzoli MD (retired), Former US Army Ophthalmology Consultant

Col Francis McVeigh OD (retired), Senior Clinical Consultant, DoD Telemedicine & Advanced Technology Research Center (TATRC)

Glenn Cockerham MD, Chief of Ophthalmology, VA Palo Alto Health Care System

Robert Read, Vision Portfolio Manager, DoD Telemedicine & Advanced Technology Research Center (TATRC)

10:10 Break

10:20 Session 1: The Nature of the Injury

Overview and Orientation

William Good MD
Christopher Tyler PhD

Pathophysiology and neuropathology of mTBI:
Similarities and differences between mTBI and
concussion, other head injuries, blast vs non-blast

Randy Kardon MD PhD

Knowledge from Animal Models

Matthew Harper PhD

Impacts on vision function – including early and
late onset -- what we know and don't know

Gregory Goodrich PhD

Blast-induced ocular and visual changes

Glenn Cockerham MD

Impacts on Hearing

Gabrielle Saunders PhD

12:20 Panel Discussion

William Good MD (Moderator)
Randy Kardon MD
Gregory Goodrich PhD
Glenn Cockerham MD
Gabrielle Saunders PhD
Stephen Heinen PhD

1:00 Lunch (provided)

2:00 Session 2: Tests, Evaluation and Assessment

mTBI Diagnosis: Objective measures of
visual dysfunction

Randy Kardon MD

Self-assessments and their effectiveness
What vision tests are currently used?

Gregory Goodrich PhD

Oculomotor function tests, photosensitivity,
accommodation and convergence tests

Suzanne Wickum OD

Potential for brain imaging in mTBI

Christopher Tyler PhD

Concussion diagnosis

Mark Lovell PhD

4:00 Panel Discussion

Arthur Jampolsky MD (Moderator)
Gregory Goodrich PhD
Suzanne Wickum OD
Dr Chung
Christopher Tyler PhD
Mark Lovell PhD or substitute
Yury Petrov PhD

5:00-6:00 Wine & Cheese Reception

Saturday March 5

8:45 am Coffee

9:15 Session 3: Therapy

Current practices	Glenn Cockerham MD
Photosensitivity management	Michael Gorin MD
Accommodative and convergence training	Kenneth Ciuffreda OD
Medical or ophthalmic interventions in the Globe	Kim Cockerham MD
Comparison with management of hearing impacts	Gabrielle Saunders PhD

11:15 Panel Discussion

John Brabyn PhD (Moderator)
Glenn Cockerham MD
Michael Gorin MD
Kenneth Ciuffreda PhD
Pia Hoenig OD
Gabrielle Saunders PhD

12:00 Future Research Funding Possibilities in mTBI James Jakorsky, NAEVR

(Panel Discussion by VA and DoD Representatives)

12:30 Summary Remarks and Adjournment

10th International Low Vision Conference,

Kuala Lumpur, Malaysia, Feb 20-24, 2011

Neurologic Vision Impairment: A New Direction for Low Vision Research and Rehabilitation

Gregory L. Goodrich
Polytrauma Clinic
VA Palo Alto Health Care System
Palo Alto CA

Neurological vision impairment frequently accompanies an acquired or traumatic brain injury. The impairments can include hemianopsia or other field loss, acuity loss, and binocular/oculomotor dysfunctions. Brain injury can also impair speech, cognition, hearing, personality, motivation, perception, and physical functioning. The common causes of neurological loss are numerous and include stroke, motor vehicle accidents, falls, sports injury, assaults, and gunshot wounds. The recent utilization of improvised explosive devices in combat and against civilian targets has highlighted blast events as a cause of brain injury.

The incidence of neurological vision impairment has not been determined, but some estimates place it as high as 20% to 40% of all brain injuries. Because brain injury is relatively common the potential number of individuals with neurological vision impairment is very large. Brain injury severity is usually considered as mild, moderate, or severe. Recent studies indicate some relationship between the severity of the injury and the resulting neurological impairment, however it is important to recognize that visual impairment can occur with any level of severity.

Neurological vision loss rehabilitation differs from low vision in significant ways. First, the impairment results not from eye disease or injury. Rather it is the result of damage to visual areas of the brain. Second, brain injury patients often present with a wide variety of deficits and neurological vision rehabilitation necessarily must take the additional deficits into account. Ideally, neurological vision rehabilitation is part of the multidisciplinary rehabilitation effort tailored to the unique needs of each patient.

In this presentation I will discuss neurological visual impairments including its causes and consequences. I will also present a discussion of current rehabilitation strategies and suggest a multidisciplinary model of care based upon experience gained at the Palo Alto Health Care System.

8th Annual World Congress on Brain, Spinal Cord Mapping & Image Guided Therapy

San Francisco, June 8-10, 2011,

Title: Brainstem/Midbrain Imaging for Oculomotor Dysfunction in Mild Traumatic Brain Injury

Christopher W. Tyler,
Head, Smith-Kettlewell Brain Imaging Center
Smith-Kettlewell Eye Research Institute
San Francisco CA

Lora T. Likova,
Smith-Kettlewell Brain Imaging Center
Smith-Kettlewell Eye Research Institute
San Francisco CA

Gregory L. Goodrich
Polytrauma Clinic
VA Palo Alto Health Care System
Palo Alto CA

Mild traumatic brain injury (mTBI) presents a diagnostic and treatment challenge because the damage to the brain is not directly assessable. In mTBI, shear stress between the cranium and the spinal column can be identified as the critical factor in generating loss of consciousness (LOC). We show that the pattern of maximal shear stresses in studies of core brain structures matches the pattern of subcortical and midbrain damage seen in magnetic resonance imaging (MRI) studies. Specifically, the shear stress is focused at the midbrain, the key brain structure for oculomotor control that may not be evident by standard brain-imaging techniques. Recent studies (e.g., Goodrich et al., 2007) have established that a high proportion (~65%) of patients diagnosed with mTBI exhibit oculomotor dysfunction (including saccadic, pursuit, vergence, and accommodative deficiencies), which have pronounced impacts on quality of life in critical tasks involving reading, driving, eye-hand coordination, media viewing, sports, etc. The complex of subcortical nuclei controlling vergence, saccadic eye movements and accommodation, though well-studied in monkeys, remains poorly understood in humans. Our special-purpose high-resolution fMRI prescription provides the first direct evidence of activation of the oculomotor pathways in the brainstem/midbrain regions affected by shear stress in mTBI. The activation strength in each oculomotor nucleus can provide an effective, non-invasive biomarker of critical deficits in the eye-movement control signals in mTBI patients.

Third Interagency Conference on Traumatic Brain Injury

June 13-15, 2011, in Washington DC

Outcome #2: Seminal Advances in TBI Research. Theme: Mild TBI and Concussion

Title: Oculomotor Dysfunction in Mild Traumatic Brain Injury

Christopher W. Tyler,
Head, Smith-Kettlewell Brain Imaging Center
Smith-Kettlewell Eye Research Institute
San Francisco CA

Lora T. Likova,
Head, Smith-Kettlewell Brain Imaging Center
Smith-Kettlewell Eye Research Institute
San Francisco CA

Gregory L. Goodrich
Polytrauma Clinic
VA Palo Alto Health Care System
Palo Alto CA

Traumatic brain injury (TBI) presents a diagnostic and treatment challenge because the damage to the brain is not directly assessable. Among the varieties of brain impact in diffuse, or mild TBI (mTBI), shear stress between the cranium and the spinal column can be identified as critical factor in generating loss consciousness (LOC), with the pattern of **maximal shear stresses** in core brain structures matching the pattern of subcortical and midbrain damage seen in magnetic resonance imaging (MRI) studies. Specifically, the focus of shear stress at the midbrain, which is the key brain structure for oculomotor control, predicts focal damage in mTBI that may not be evident by standard brain-imaging techniques.

Recent studies (e.g., Goodrich et al., 2007) have established that a high proportion (~65%) of patients diagnosed with mTBI exhibit binocular vision dysfunctions (including saccadic, pursuit, vergence, and accommodative instabilities). Such disruptions of binocular eye movement control often results in serious deficits of binocular coordination and/or double vision, which have pronounced impact on quality of life in critical tasks involving reading, driving, eye-hand coordination, media viewing, sports activities, etc. Effective treatment of these oculomotor problems requires accurate diagnosis of the complex of subcortical pathways controlling binocular coordination.

The complex of subcortical nuclei controlling vergence, saccadic eye movements and accommodation, though well-studied in monkeys, remains poorly understood in humans. We have developed a special-purpose high-resolution fMRI prescription to provide the first direct evidence of activation of the oculomotor pathways in the subcortical/midbrain regions affected by shear stress in mTBI. Accurate knowledge of the organization of the pathways is critical to identifying the specific loci to be targeted for analysis of deficiency resulting from the

mTBI. The activation strength in each oculomotor nucleus can provide an effective, non-invasive biomarker of critical deficits in the eye-movement control signals in mTBI patients.

The learning objectives for the presentation are:

1. To provide an enhanced understanding of the physical mechanisms leading to mTBI with LOC.
2. To highlight how visual aspects of mTBI negatively affect many aspects of everyday life.
3. To convey the value of structural and functional MRI in tracing mTBI effects on brain nuclei.
4. To explain the value of oculomotor indices as biomarkers for covert mTBI damage.

The reported research will transform the field because the provision of an explicit physical mechanism for the loci of subcortical damage in mTBI with LOC provides a series of targets for extended evaluation of affected functions. Once the affected functions are identified, focused remediation strategies can be developed. For example, reading disability is a large-scale problem faced by many mTBI sufferers; if one mechanism for reading disabilities is degradation of binocular coordination, remediation can focus on improving binocular coordination, which would not have been attempted if it was attributed to a cognitive deficit.

The implications for future research are to open up the development of successful diagnostics, medical treatments and rehabilitation of mTBI guided by a detailed understanding of the loci brain injury that causes the critical aspects of the experienced dysfunctions.



Translational Research: Seeing the Possibilities

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Program#/Poster#:	4869/D812
Abstract Title:	Analysis of Human Vergence Dynamics
Presentation Start/End Time:	Wednesday, May 09, 2012, 1:45 PM - 3:30 PM
Session Number:	456
Session Title:	Eye Movements
Location:	Hall B/C
Reviewing Code:	182 eye movements - EY
Author Block:	<i>Christopher W. Tyler, Anas Elsaid, Lora Likova, Spero Nicholas.</i> SK Brain Imaging Center, Smith-Kettlewell Eye Research Institute, San Francisco, CA.
Keywords:	521 eye movements, 747 vergence, 619 ocular motor control
Abstract Body:	<p>Purpose: Binocular vergence is controlled by a mix of disparity, accommodative and proximal vergence cues. Peak vergence velocities are an order of magnitude slower than conjugate saccades, with similar onset latencies, and frequent saccadic intrusions particularly for asymmetrical vergence movements. Here we estimate the distribution of symmetrical vergence dynamics parameters in a large population of fifty normal volunteers.</p> <p>Methods: The symmetrical disparity vergence stimulus consisted disparity jumps of $\pm 2^\circ$ of a combined central fixation target and surrounding random-dot field at unpredictable intervals varying from 2-3 s. The study also included 0.25 Hz sinusoidal vergence and versional tracking tasks for the same stimuli. Binocular eye movements were recorded with a dual infrared limbal eye tracker. The subjects were assessed for stereopsis, strabismus and a past history of traumatic brain injury (TBI).</p> <p>Results: Most subjects were able to perform the disparity jump and sinusoidal tracking tasks with approximately symmetrical vergence movements, with relatively few saccadic intrusions. For the disparity jumps, the peak vergence velocities averaged about 8 deg/s for convergence (and marginally slower for divergence), being thus a factor of ~5 slower than saccades for this amplitude (1° in each eye), having durations of about 400 ms. A substantial subpopulation (with no strabismus or TBI) showed an inability to make prompt divergence movements in one eye, using an anomalous 'inverse priming' strategy for divergence, involving an interplay of convergence and glissade movements followed by larger uniocular divergence to achieve the required divergence angle. Mostly, the time courses of these anomalous movements were non-saccadic with typical vergence dynamics, despite being predominantly uniocular. A different subgroup with a history of TBI had either convergence or divergence movements (or both) of much reduced velocity and increased duration (500-2000 ms).</p> <p>Conclusions: There was a wide variety of 'normal' vergence dynamics, from matching convergence/divergence dynamics to anomalous inverse priming strategies to overcome uniocular vergence deficits. Subject with a history of recent TBI dramatic slowing of the vergence dynamics. The results are important for understanding the range of binocular coordination dynamics that should be expected in the normal population and the analysis of oculomotor control deficits in the TBI population.</p>
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